REMARKS

Claims 1, 8, 10, 17-19, 27, and 28 have been amended

Claims 6, 16, and 26 have been canceled. Such cancellation is without prejudice to further prosecution of these claims in one or more continuing applications.

Claims 31-39 have been added herein.

Claims 1-39 are pending. Favorable reconsideration is respectfully requested.

Newly added claims 31-39 enjoy explicit support throughout the specification and in the claims as originally filed. Specifically, new Claims 31-35 are supported by Claims 1-18 as originally filed and in the specification at page 9, lines 10-15 (which discusses the introduction of an *ortho* amino moiety into a tyrosine residue of an acyl carrier protein (ACP)). Similarly, Claims 36-39 (drawn to a kit) are supported by Claims 19-28 as originally filed, and by the above-noted passage from the specification. No new matter is added.

The following remarks address the issues presented in the Office Action in order of their appearance.

Rejection of Claims 1-30 Under 35 USC §112, First Paragraph (Enablement):

This rejection is respectfully traversed because the specification provides ample information to allow a person of ordinary skill in the art to practice the invention as broadly as it is claimed.

Specifically, Claim 1 as originally submitted requires a labeled acyl carrier protein (ACP) having bonded thereto a non-radioactive label. Applicants respectfully submit that: (1) the specification provides ample information to enable one to select a suitable ACP for use in the invention (both via working examples and a large list of suitable sources); (2) the specification provides ample information to enable one to select a suitable non-radioactive label (both via working examples and a large list of suitable labels) ; and (3) the specification provides ample information to enable one to attach the label to the ACP.

As a preliminary matter, some clarification of the claimed invention is in order. The Office states, at the bottom of page 2 of the Office Action, that the invention is

enabling for labeled apo-, holo-, and acylated-ACP, derived from *E. coli*, wherein the non-radioactive labeled product is "nitroTyr-ACP, aminoTyr-ACP, or dansylaminoTyr-ACP." Only the last product in the quoted list, dansylaminoTyr-ACP, is a product encompassed by the present claims. DansylaminoTyr-ACP is an ACP having bonded thereto a non-radioactive label. In contrast, nitroTyr-ACP and aminoTyr-ACP are intermediate products.

See, for example, the passage spanning page 11, line 12 of the specification, to page 12 line 22. Here, the specification describes how the non-radioactive label is attached to a modified tyrosine residue in the ACP. The phenyl side-chain of a tyrosine moiety of an unmodified ACP is first nitrated (to yield nitroTyr-ACP). The nitroTyr-ACP is then reduced to yield a convenient *ortho*-amino tyrosine residue within the ACP. The amino moiety added to the tyrosine residue provides a convenient reactive site that allows any number of non-radioactive labels to be attached quickly and easily to the ACP.

See also the "Overview" section of the specification, at page 9, lines 5-15:

> To facilitate further studies of Δ9D substrate selectivity, a specific site of attachment of a fluorescent probe to ACP was desired. Since *E. coli* ACP contains at least one of every polar and charged amino acid, modification strategies directed toward these amino acids were unlikely to give the desired unique labeling....
>
> The *o*-nitration of tyrosine with tetranitromethane followed by reduction with sodium dithionite produces *o*-aminotyrosine, and this introduces a new amine group into the protein with a unique pK_a value of ~4.75 [citations omitted]. Because the sole Tyr residue (Tyr71) of *E. coli* ACP is near the *C*-terminus, and because modification of the *C*-terminus of spinach ACP did not alter reactivity with ACPS, AAS, or Δ9D [citations omitted], Tyr71 was targeted for chemical modification and subsequent attachment of a dansyl group.

See also the paragraph at page 3, lines 2-10 of the specification:

> A third embodiment of the invention is a method of making a holo-acyl carrier protein having a non-radioactive label affixed thereto. The method comprises first reacting an apo-ACP having at least one tyrosine residue with a chemical reagent capable of covalently bonding an amino moiety to the tyrosine residue. This yields an apo-ACP having an amino-modified tyrosine moiety. A non-radioactive label is then covalently bonded to the amino-modified tyrosine

moiety, thereby yielding an apo-ACP having a non-radioactive label covalently bonded thereto.

Applicants simply want to clarify for the record that nitroTyr-ACP and aminoTyr-ACP are not compounds encompassed by the present claims. They are intermediate compounds generated to facilitate the easy attachment of the non-radioactive label to the ACP.

Regarding the source of the ACP to be modified, the Office is correct that the claims encompass ACPs from any source. This is the Applicants' intent. Applicants submit that this breadth does not run afoul of the enablement requirements of §112, first paragraph because the application contains ample information about the sources for suitable ACPs and because ACPs are a very highly conserved, art-recognized class of proteins. Therefore, the term "acyl carrier protein" clearly conveys to a person of ordinary skill in the art a well-defined genus of compounds, all of which have substantially identical reactivity.

Regarding Applicants' specification itself, the specification includes an entire section given over to a discussion of ACPs that can be used in the present invention. See the specification at page 6, line 15, to page 7, line 4:

> Acyl Carrier Protein (ACP):
>
> As used herein, the term acyl carrier protein (ACP) denotes any acyl carrier protein, derived from any source whatsoever (naturally-derived, semi-synthetic, fully-synthetic) that includes at least one tyrosine residue. In many ACPs, a tyrosine residue is located in a position near to the C-terminal, as is the case with *E. coli* ACP. In other cases, a tyrosine residue is located near to the conserved serine residue that acts as the site of phosphopantetheinylation. In a limited number of cases, tyrosine residues are present in both locations. A tyrosine residue is found in the ACPs of every bacterial genus that has an entry in GenBank. Thus, it is very likely that other organisms not presently cataloged within GenBank will also have ACPs that include a suitable tyrosine residue. Organisms cataloged with GenBank that have an ACP having at least one tyrosine residue (and are thus ACPs that can be used in the present invention) include: *Bacillus*, *Clostridium*, *Haemophilus influenza*, *Klebsiella pneumoniae*, *Mycobacterium*, *Mycoplasma pneumonia*, *Neisseria meningitidis*, *Pseudomonas aeruginosa*, *Salmonella typhimurium*, *Shigella dysenteria*, *Streptococcus pyogenes*, *Treponema pallidum*, and *Vibrio cholerae*. Other organisms that are not cataloged within GenBank, but that are believed to have ACPs that contain at least one tyrosine residue include, without limitation: *Borellia burgdorferi*, *Bortedella*, *Brucella*,

> *Corynebacterium, Listeria monocytogenes, Staphylococcus*, and *Yersinia pestis.*
>
> Thus, any ACP isolated from or derived from any of these sources and modified to contain a non-radioactive label as described herein, falls within the scope of the present invention.

As evidenced by the quoted passage, the specification clearly includes a rather extensive list of potential sources for suitable ACPs. Thus, a person of ordinary skill in the art has been provided an exemplary list of ACPs, as well as the name of a publicly-accessible database (GenBank) where additional ACPs can be found. Any number of ACP proteins can be found by searching GenBank, a database that is accessible to the public without cost and is fully searchable.

Also, as noted above, ACPs are a remarkably conserved class of proteins. Because ACPs are so highly conserved, their chemistry and reactivity is also highly conserved. As objective evidence of this fact, Applicants submit for the Office's consideration an article by Worsham et al., attached hereto as Exhibit 1 and incorporated by reference (Worsham et al. (2003) *Biochemistry* 42:167-176). Citing three references that pre-date the filing of the present application, Worsham et al. note, at page 167, right-hand column:

> Given its crucial roles in metabolism across the richness of life, the high degree of conservation of ACP's primary structure **is not surprising**. The three-dimensional structure of *Escherichia coli* ACP **is the prototype of bacterial and plant ACP structures**.

This reference is quite clear. The high degree of ACP's primary structure (that is, it's amino acid sequence) "**is not surprising**." Further still, the authors state that the *E. coli* ACP in particular is the paradigm, the "prototype," of bacterial and plant ACP structures. In short, the authors clearly indicate that the *E. coli* ACP is a suitable representative for **all** bacterial and plant ACP structures. Thus, it is equally **unsurprising** for a person of ordinary skill in the art to expect that because the amino acid sequence of ACPs are so highly conserved, ACPs from any source would have essentially identical reactivity.

As further evidence of the conserved nature of ACPs, Applicants submit for the Office's consideration Exhibit 2, attached hereto and incorporated herein, which is a demonstration of the Clustalw software for multiple sequence alignments. Exhibit 2 was

obtained from the website maintained by the Evolutionary, Ecological, and Environmental Genomics Group of Idaho State University at www.egg.isu.edu; see specifically www.egg.isu.edu/biocourses/bios599/projects/lyla_html. Of note in Exhibit 2 is that it presents a nucleic acid and amino acid sequence alignment, using the Clustalw software, for ACPs from six different bacterial species: Haemophilus, Vibrio, Leptospira, Clostridium, Lactobacillus, and Mycoplasma. The amino acid alignment for the ACPs from these six different species is presented in full on page 5 of Exhibit 2. This multiple sequence alignment reveals ACPs to be very highly conserved across distinct species.

Applicants also note that the Office in incorrect in implying that only *E. coli* ACP is exemplified in the specification. Specifically, see page 10, line 8, to page 11, line 10 of the specification. Here, the expression of ACPs from spinach, *Streptomyces*, and *E. coli* are discussed. (The ACPs were co-expressed with ACP-synthase (ACPS).) Table 1 at page 10 reports the results of using different types of growth media to maximize expression of the recombinant ACPs. As shown in Table 1, Luria-Bertani medium worked best (from among those tested) to express recombinant ACPs from spinach, *Streptomyces*, and *E. coli*.

In light of the information presented in the specification itself, as well as the evidence of the information known by one of skill in the art presented in Exhibits 1 and 2, Applicants explicitly traverse the statement at the top of page 4 of the Office Action. Here, the Office concludes that it would be beyond the scope of a skilled artisan to use any ACP other than the ACP from *E. coli*. In support of this position, the Office states

> This is because of the diverse ACP source(s) having varying structures and function depending upon its origin. Thus, when the new ACP which is of different structure and function (physico/chemical) is subjected to a specific chemical modification(s) of amino acid(s) based upon the experimentation of *E. coli* ACP, the chances of success are unpredictable.

The above-quoted statement is wholly unsupported by any prior art references or objective scientific evidence support.

In contrast to this statement, as shown by Exhibits 1 and 2, one of skill in the art would expect exactly the opposite: ACPs are extraordinarily conserved, a fact that the authors of Exhibit 1 deemed "not surprising." Thus, one of skill in the art would expect

ACPs from any source to react in a very similar (if not identical) fashion. Rather than being unpredictable, the chemistry presented in the specification is highly predictable, and conveys ample information to enable a person of ordinary skill to repeat the process successfully using an ACP from any source.

Regarding the selection of a suitable non-radioactive label, Applicants respectfully note that the specification contains an exhaustive list of suitable non-reactive labels in the table presented at pages 7 and 8 of the specification. Note that all of the non-radioactive labels listed in the table are **commercially available**. Most of them are available in kit form, wherein the kit includes all of the reagents required to label a protein or polypeptide substrate. The table includes Molecular Probes' catalog number for ease of reference. The table even presents a CAS registry number, where known, for the various non-radioactive labels. Specifically mentioned within the table are **commercially available kits** to affix a rhodamine label, a Texas Red label, a tetramethylrhodamine label, a fluorescein label, and a FITC label to a protein substrate. Applicants cannot overemphasize that these kits are commercially available. Any chemist worth his salt can simply call Molecular Probes and request a kit. Moreover, Molecular Probes is only one of a great many commercial companies that provide kits to affix a non-radioactive label to a protein substrate. For example, Boehringer-Mannheim, Invitrogen, NEN, Promega, and Qiagen all market similar kits.

Further still, extensive information about how to use the kits is provided by the commercial suppliers. After all, that is their business. Molecular Probes, for example, goes to great lengths to distribute its product literature far and wide. The kit instructions are easily obtained on-line or can be requested over the phone and are quite detailed. As evidence, see Exhibits 3 through 8, attached hereto and incorporated herein. These documents were obtained on-line at Molecular Probes' web site, www.probes.com.

Exhibit 3 is Section 1.2 of a handbook published by Molecular Probes. This section of the handbook explicitly addresses how to use Molecular Probes' kits for labeling proteins and nucleic acids. Exhibit 4 is the product literature for Molecular Probes' FluoReporter® Rhodamine Red protein labeling kit, which is referenced in the last entry at

the bottom of page 7 of the present specification. Exhibit 5 is the product literature for Molecular Probes' FluoReporter® Texas Red® -X protein labeling kit, which is referenced in the top entry of page 8 of the specification. Exhibit 6 is the product literature for Molecular Probes' FluoReporter® Tetramethylrhodamine protein labeling kit, which is referenced in the second entry of page 8 of the present specification. Exhibit 7 is the product literature for Molecular Probes FluoReporter® Fluorescein-EX protein labeling kit, which is referenced in the fifth entry of page 8 of the present specification. Exhibit 8 is the product literature for Molecular Probes FluoReporter® FITC protein labeling kit, which is referenced in the sixth entry of page 8 of the present specification.

In short, these kits, as well as the others mentioned at pages 7 and 8 of the specification, are commercially available, distributed worldwide, and exhaustively documented. The specification thus present extensive data, more than sufficient, to enable a person of ordinary skill in the art to select a suitable non-radioactive probe and to attach the same to an ACP.

The specification also presents a general method to attach a non-radioactive probe to an ACP having a tyrosine residue. See page 9, lines 10-15, and page 11, line 12, to page 12, line 22 of the specification. By introducing an amine functionality having a unique pKa value to the tyrosine residue, simple acid-base chemistry can be used to affix a label to the reactive amine moiety. Because of the unique pKa of the introduced amine group (4.75), the pH of the reaction buffer controls the reactivity of that specific amine group. The reaction is thus general and will work with any ACP having a tyrosine group.

Lastly, the specification includes a complete, start-to-finish working example of the invention, from plasmid construction (see Example 1), to fermentation protocols (see Example 2), to ACP purification (see Example 3), to nitration of the tyrosine residue (see Example 4), to reduction of the nitro group to yield an amino-tyrosine residue (see Example 5), to dansylation of the amino-tyrosine group to yield an ACP having a non-radioactive moiety attached thereto (see Example 6). The Examples go in to include demonstrations of *in vivo* phosphopantetheinylation and acylation of the dansyl-ACP

produced according to Examples 1 to 6 (see Example 7). The labeled proteins so produced were then purified and extensively characterized (see Examples 8 through 13).

Applicants therefore submit that the application fully enables a person of ordinary skill in the art to practice the invention as broadly as it is claimed, in full satisfaction of the enablement requirement of 35 USC §112, first paragraph. It is therefore respectfully submitted that the rejection of Claims 1-30 under 35 USC §112, first paragraph (enablement) is improper. Withdrawal of the rejection is requested.

Rejection of Claims 1-30 Under 35 USC §112, First Paragraph (Written Description):

This rejection is traversed, largely for the same reasons articulated in the prior section. While the enablement and written description requirements of §112 are separate, they are closely related. Thus, the comments in the prior section are incorporated herein with respect to the written description requirement. The specification provides ample written description of the invention and how to make, use and practice the invention, so as to assure that Applicants were in possession of the claimed invention at the time the application was filed.

Specifically addressing the written description requirement itself, Applicants traverse the rejection because defining a generic term by listing a number of exemplary species that fall within the generic term is a perfectly valid and **approved** approach to defining a generic term. See MPEP §2164.08 and *In re Marzocchi*, 169 USPQ 367, 370 (CCPA 1971): "How a teaching is set forth, by specific example or broad terminology, is not important." (Emphasis added.) Moreover, what is well-known in the art is best omitted from the specification. MPEP §2164.08 and *In re Buchner*, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). Further still, Applicants **are not** required to describe and test every single species falling within a generic claim. See *In re Angstadt* 190 USPQ 214 (CCPA 1976). The specification provides extensive written documentation of suitable ACPs, suitable non-radioactive labels, and how to affix the labels to the ACPs. By listing quite a large number of species falling within each respective genus ("ACP" and "non-radioactive label") Applicants submit that the specification complies with the written

description requirement as per the guidelines presented in the MPEP and the controlling case law.

For example, Applicants use the generic term "non-radioactive label." To define "non-radioactive label," Applicants specifically recite a large number of species that fall within the generic terms "non-radioactive label." Applicants list a commercial supplier for the suitable labels. Applicants list the catalog numbers of the labels. Applicants list the Chemical Abstracts Service registry numbers for the labels. All of this information is presented in the specification in the table starting at page 7, and reproduced below:

Molecular Probes' Catalog Number	Description (All trademarks property of Molecular Probes)	Chemical Abstracts Number (where available)
F2610	FluoReporter® Biotin-XX Protein Labeling Kit	89889-52-1
F6153	FluoReporter® Oregon Green® 488 Protein Labeling Kit	198139-51-4
F-6155	FluoReporter® Oregon Green® 514 Protein Labeling Kit	N/A
F-6161	FluoReporter® Rhodamine Red™-X Protein Labeling Kit	N/A
F-6162	FluoReporter® Texas Red®-X Protein Labeling Kit	216972-99-5
F-6163	FluoReporter® Tetramethylrhodamine Protein Labeling Kit	246256-50-8
F-6347	FluoReporter® Mini-biotin-XX Protein Labeling Kit	N/A
F-6348	FluoReporter® Biotin/DNP Protein Labeling Kit	N/A
F-6433	FluoReporter® Fluorescein-EX Protein Labeling Kit	N/A
F-6434	FluoReporter® FITC Protein Labeling Kit	3326-32-7
R-363	resorufin, sodium salt	635-78-9
A-191	7-amino-4-methylcoumarin	26093-31-2
C-2110	CellTracker™ Blue CMAC (7-amino-4-chloromethylcoumarin)	N/A

Molecular Probes' Catalog Number	Description (All trademarks property of Molecular Probes)	Chemical Abstracts Number (where available)
C-12881	CellTracker™ Blue CMF_2HC (4-chloremethyl-6,8-difluoro-7-hydroxycoumarin)	N/A
C-183	3-cyano-7-hydroxycoumarin	19088-73-4
D-6566	6,8-difluoro-7-hydroxy-4-methylcoumarin (DiFMU)	215868-23-8
E-6578	ELF® 97 alcohol	N/A
F-1300	fluorescein	2321-07-5
H-6482	7-hydroxy-9*H*-(1,3-dichloro-9,9-dimethylacridin-2-one) (DDAO)	118290-05-4
H-189	7-hydroxy-4-methylcoumarin	90-33-5
P12925	5-(pentafluorobenzoylamino)fluorescein (PFB-F)	N/A
R-6479	rhodamine 110 (R110)	13558-31-1
T-659	β-trifluoromethylumbelliferone (7-hydroxy-4-trifluoromethylcoumarin)	575-03-1

Methods to affix these labels to a protein substrate are exceedingly well known to those skilled in the art, as evidenced by Exhibits 3-8, attached hereto. As noted earlier, what is well-known in the art is best omitted from the specification. MPEP §2164.08 and *In re Buchner*, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991).

The specification also presents a general method to attach a non-radioactive probe to an ACP having a tyrosine residue. See page 9, lines 10-15, and page 11, line 12, to page 12, line 22 of the specification. By introducing an amine functionality having a unique pKa value to the tyrosine residue, simple acid-base chemistry can be used to affix a label to the reactive amine moiety. Because of the unique pKa of the introduced amine group (4.75), the pH of the reaction buffer controls the reactivity of that specific amine group. The reaction is thus general and will work with any ACP having a tyrosine group.

The same holds true for Applicants written description of suitable ACPs. Defining a generic term by listing a number of exemplary species that fall within the generic term is

a perfectly valid and **approved** approach to defining a generic term, MPEP §2164.08. With regard to the ACP, the specification contains the following passage at page 6, line 15, to page 7, line 4:

> As used herein, the term acyl carrier protein (ACP) denotes any acyl carrier protein, derived from any source whatsoever (naturally-derived, semi-synthetic, fully-synthetic) that includes at least one tyrosine residue. In many ACPs, a tyrosine residue is located in a position near to the C-terminal, as is the case with *E. coli* ACP. In other cases, a tyrosine residue is located near to the conserved serine residue that acts as the site of phosphopantetheinylation. In a limited number of cases, tyrosine residues are present in both locations. A tyrosine residue is found in the ACPs of every bacterial genus that has an entry in GenBank. Thus, it is very likely that other organisms not presently cataloged within GenBank will also have ACPs that include a suitable tyrosine residue. Organisms cataloged with GenBank that have an ACP having at least one tyrosine residue (and are thus ACPs that can be used in the present invention) include: *Bacillus*, *Clostridium*, *Haemophilus influenza*, *Klebsiella pneumoniae*, *Mycobacterium*, *Mycoplasma pneumonia*, *Neisseria meningitidis*, *Pseudomonas aeruginosa*, *Salmonella typhimurium*, *Shigella dysenteria*, *Streptococcus pyogenes*, *Treponema pallidum*, and *Vibrio cholerae*. Other organisms that are not cataloged within GenBank, but that are believed to have ACPs that contain at least one tyrosine residue include, without limitation: *Borellia burgdorferi*, *Bortedella*, *Brucella*, *Corynebacterium*, *Listeria monocytogenes*, *Staphylococcus*, and *Yersinia pestis*.
>
> Thus, any ACP isolated from or derived from any of these sources and modified to contain a non-radioactive label as described herein, falls within the scope of the present invention.

As evidenced by the quoted passage, the specification clearly includes a rather extensive list of potential sources for suitable ACPs. Thus, a person of ordinary skill in the art has been provided an exemplary list of ACPs, as well as the name of a publicly-accessible database (GenBank) where additional ACPs can be found. Any number of ACP proteins can be found by searching GenBank, a database that is accessible to the public without cost and is fully searchable.

Also, as noted above, ACPs are a remarkably conserved class of proteins. Thus, in terms of satisfying the written description requirement, Exhibit 1 explicitly states that the amino acid sequence of ACPs are conserved to a "high degree," and further that this high

degree of conservation "is not surprising." Further still, the authors of Exhibit 1 note that the ACP from E. coli is the "prototype" for all other bacterial and plant ACPs.

Thus, contrary to the wholly unsupported conclusion presented at the middle of page 5 of the Office Action, the genus of ACPs <u>is not</u> variable. The genus "ACP" is, as evidenced by Exhibits 1 and 2, **<u>highly conserved and invariable</u>**.

Applicants also explicitly traverse the statement appearing at page 5, lines 11-14 of the Office Action:

> The specification does not contain any disclosure of the function of all the labeled carrier proteins obtained from a combination of representative ACPS of the diverse species of the plant & animal kingdoms and there [sic] chemical modifications, within the scope of the claimed genus.

Applicants simply are not required to provide this information in order to satisfy the written description requirement. The claimed compounds are modified ACPs. They function as ACPs (see page 2, lines 19-20). If they have other functions in addition thereto, they are still ACPs. If some function "better" than others, that fact is irrelevant to the both the written description and enablement requirements. There is no requirement that all of the compounds falling within a claimed genus exhibit the same degree of efficacy in order to satisfy the requirements of §112.

In conclusion, Applicants have included in the specification very extensive lists of sources for suitable ACPs, as well as suitable non-radioactive labels that can be used in the invention. Having done so, Applicants respectfully submit that the written description requirement of 35 USC §112, first paragraph, have been satisfied.

Applicants therefore submit that the rejection of Claims 1-30 under 35 USC §112, first paragraph (written description) is untenable. Withdrawal of the same is respectfully requested.

Rejection of Claims 8, 17, and 27 Under 35 USC §112, Second Paragraph:

This rejection is believed to have been overcome by appropriate amendment to Claims 8, 17, and 27, in accordance with the Examiner's recommendation. Specifically, the various acronyms have been removed from these claims and the full spelling inserted.

It is respectfully requested that this rejection be withdrawn.

Rejection of Claims 1 and 19 Under 35 USC §102(b) Over Abita et al. (1971) *Eur. J. Biochem* 23:412-420:

This rejection is believed to have been overcome by appropriate amendment to Claims 1 and 19. Specifically, as amended, these two claims require that the non-radioactive label be a fluorophore. Because the Abita et al. reference neither discloses nor suggests affixing a fluorophore to an ACP, this rejection has been overcome. Withdrawal of the same is respectfully requested.

Rejection of Claims 1-3, 5 and 19 Under 35 USC §102(b) Over Hill et al. (1995) *Protein Expression & Purification* 6(4):394-400:

This rejection is believed to have been overcome by appropriate amendment to Claims 1 and 19. Specifically, as amended, these two claims require that the non-radioactive label be a fluorophore. Because the Hill et al. reference neither discloses nor suggests affixing a fluorophore to an ACP, this rejection has been overcome. Withdrawal of the same is respectfully requested.

Rejection of Claims 1-30 Under 35 USC §102(b) Over Haas et al. (2000) *Protein Expression and Purification* 20(2):274-284:

This rejection is believed to have been overcome by the Rule 131/132 Declaration of inventors Brian G. Fox and Jeffrey A. Haas, submitted herewith. As discussed below, Applicants submit that the Declaration antedates the Haas et al. reference, thereby rendering it unavailable as prior art against the present application.

At paragraph 1 of their Declaration, Drs. Haas and Fox state that they are co-inventors of the subject matter claimed in the present application. At paragraph 2 of their Declaration, Drs. Haas and Fox state that they are co-authors of the Haas et al. paper that is relied upon in the rejection. At paragraph 3, Drs. Haas and Fox state that the Haas et al. paper, which is dated November 2000, appeared less than one year after the filing date of the subject application.

In paragraphs 4 and 5 of their Declaration, Drs. Haas and Fox state that they conceived of the present invention, reduced the same to practice, wrote a paper describing the invention, and submitted the paper for publication in the journal *Protein Expression and Purification*. This submission ultimately matured into the applied reference noted above. The Declaration includes an Exhibit of the paper that Hass and Fox submitted to the journal. Exhibit A of the Declaration is substantially (if not exactly) identical in content to the Haas et al. publication. At paragraph 5 of the their Declaration, Haas and Fox note that Exhibit A to their Declaration was produced prior to November 1, 2000.

In light of the Declaration, Applicants respectfully submit that the Haas et al. paper has been antedated and is therefore not available as prior art with respect to the claimed invention.

Withdrawal of this rejection of Claims 1-30 in view of the Haas et al. paper is respectfully requested.

CONCLUSION

In light of the above amendment, remarks, and the Rule 131/132 Declaration filed herewith, Applicants respectfully submit that the application is now in condition for allowance. Early notification of such action is earnestly solicited.

Respectfully submitted,

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